

### **REMARKS**

Prior to the present amendment, claims 26-28 and 33-35 were pending. Claims 1-20, and 29-32 were previously canceled. No new amendments to the claims have been made. No new matter has been added. Accordingly, claims 26-28, 33-35 remain under consideration.

#### **Rejection under 35 U.S.C. § 103 over Eschenfelder and Baldwin**

On page 3 of the office action, the examiner rejects claims 26-28 and 33 as being unpatentable under U.S.C. § 103(a) over Eschenfelder (*US 4,944,943*) and Baldwin (*US 5,098,707*). In response to applicants' arguments of January 21, 2009, the examiner alleges on page 8 of the office action that "it is clear from the teachings of Eschenfelder that the use of an antithrombotic such as streptokinase for the treatment of a vascular disease such as hemorrhoid disease was known at the time of the invention." The examiner continues by stating that one of skill in the art "would therefore have understood that an antithrombotic agent could have been formulated as described by Baldwin in the absence of any additional active components for use in a method of treating hemorrhoid disease.

Applicants respectfully disagree.

Eschenfelder teaches that his "present invention relates to a mixture of a substance having thrombolytic activity and of an antithrombotic substance" (col. 1, lines 23-25). In addition, the only reference to treatment of "hemorrhoidal thrombosis" in Eschenfelder concerns "the mixture" (col. 2, lines 38-41):

The mixture is therefore suitable for the treatment of thromboses of any type, such as thrombophlebitis, hemorrhoidal thrombosis, pulmonary embolism and infarct.

Baldwin fails to compensate for the deficiencies of Eschenfelder. As acknowledged by the examiner on page 4 of the office action, Baldwin is devoid of any disclosure or suggestion of a method for treating hemorrhoid disease.

In the passage cited by the examiner (i.e., col. 24, lines 1-35), Baldwin discloses preparation of suppositories with conventional carriers. However, in the paragraph immediately preceding the passage that was cited by the examiner, Baldwin describes such compositions as a mixture. See col. 23, lines 65-68 of Baldwin:

Compositions to be employed in the practice of the present invention whether parenteral, oral or suppository compositions comprises an imidazole compound in a pharmaceutically acceptable carrier.

(emphasis added).

The examiner also cites the abstract of Baldwin, which also teaches a mixture:

Compositions useful for thrombolytic therapy comprising a plasminogen activator such as tPA or streptokinase together with an imidazolium salt...

Accordingly, the methods described in both Eschenfelder and Baldwin individually and in combination require an additional active compound for use in treatment, and they do not read upon the claimed compositions "consisting essentially of" a thrombolytic protein. "All words in a claim must be considered in judging the patentability of that claim against the prior art."

*MPEP § 2143.03.*

“The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art.” *MPEP* § 2143.01. In the present case, the mere fact that thrombolytic proteins can be omitted from Eschenfelder and Baldwin does not obviate the claimed invention because none of the cited references provided any evidence of predictability in an effective method for treatment of hemorrhoid disease in a human through rectal administration. Every one of the methods of treatment disclosed in Eschenfelder and Baldwin relates to a composition that includes an additional active compound.

In fact, the modification of the Eschenfelder and Baldwin references as proposed by the examiner would not have yielded any predictable results concerning treatment of hemorrhoid disease through rectal compositions consisting essentially of thrombolytic proteins. The Yamamoto reference submitted with the IDS of January 21, 2009 states the possibility of:

...incomplete absorption [of peptides and protein drugs]...due to a combination of poor membrane permeability and metabolism at the absorption site. Thus, a number of absorption enhancers have been utilized for improving rectal absorption of larger polypeptides and proteins.

(p. 276 of Yamamoto). The Yamamoto reference also indicates the presence of proteases at the area of rectal absorption such as trypsin (p. 282, Figure 3, and p. 276 first full paragraph on the left-hand column of Yamamoto).

Moreover, the Castellanos-Serra reference (*Electrophoresis*, 2002 Jun;23(11):1745-53), which will be submitted in an IDS, states on page 1751 that streptokinase is “a 47 kDa protein that has proven to be highly sensitive to proteolytic degradation, even under native conditions. There are several reasons for this high susceptibility towards proteolysis: this 414 amino acids protein has 52 tryptic...cleavage sites...”

Thus, there was an expectation of incomplete absorption and/or proteolysis of the thrombolytic proteins by the proteases at the site of rectal administration. The thrombolytic proteins were known to be highly susceptible to proteolytic degradation, and rectal administration of protein drugs has been hampered by the presence of proteases. There was no predictability regarding rectal administration of a composition consisting essentially of a thrombolytic protein.

Contrary to the examiner's allegations, mere existence of a composition consisting essentially of a thrombolytic protein at the time of the invention is not evidence that it was predictable in the art to administer rectally such a composition in a method to treat hemorrhoid disease effectively. The claims require that the treatment is effective.

The examiner has not cited to any disclosure in either Eschenfelder or Baldwin that rectal compositions consisting essentially of thrombolytic proteins would predictably treat hemorrhoid disease. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." *MPEP § 2143.01*. Based on Eschenfelder and Baldwin, nothing was predictable regarding treatment of hemorrhoid disease by rectally administering a thrombolytic protein without an additional active compound.

Eschenfelder teaches intraarterial, intravenous, subcutaneous, and infusion administration of the "mixture" (col. 2, lines 22-25). Eschenfelder is completely devoid of any teaching regarding rectal administration of any composition, whether a mixture or one consisting essentially of a thrombolytic protein.

Baldwin fails to compensate for the deficiencies of Eschenfelder. The only disclosure regarding rectal administration is in Baldwin, which concerns administering "suppository compositions [that] comprise an imidazole compound in a pharmaceutically acceptable carrier" (col. 23, lines 65-68, Baldwin).

None of the disclosures, data, or examples in Eschenfelder and/or Baldwin addresses any of the unpredictable factors with respect to rectal administration of thrombolytic proteins (e.g., the presence of proteases). None of the examples in Baldwin and Eschenfelder shows the efficacy of any composition in the treatment of a thrombotic event following rectal administration of a composition consisting essentially of a thrombolytic protein.

Lastly, there lacks any suggestion or motivation to make the proposed modification based on the cited references. Eschenfelder states:

The present invention relates to a mixture of a substance having thrombolytic activity and of an antithrombotic substance...The mixture is therefore suitable for the treatment of...hemorrhoidal thrombosis.

Baldwin states:

“Compositions useful for thrombolytic therapy comprising a plasminogen activator such as tPA or streptokinase together with an imidazolium salt...”

(abstract). An omission of the additional active compound in the compositions of Eschenfelder and/or Baldwin would render both references inoperable for their respective intended methods of treatment.

Nothing in Eschenfelder and/or Baldwin evidences that an omission of the respective additional active compound would predictably treat hemorrhoid disease. As stated above, none of the unpredictable factors concerning rectal administration of a protein were addressed in either reference. See *MPEP* § 2143.01 (“If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification”).

Accordingly, the combination of cited references fails to obviate every element of the claims; the mere fact that the references can be modified does not render the claimed invention obvious when rectal administration of a thrombolytic protein would have been unpredictable; and there is no suggestion or motivation to make the proposed modification of omitting additional active components since the proposed modification would render Eschenfelder and Baldwin inventions unsatisfactory for its intended purpose. Therefore, the cited references, individually and in combination, fail to obviate the claimed invention under 35 U.S.C. § 103. Applicants respectfully request reconsideration and withdrawal of the rejection.

**Rejection under 35 U.S.C. § 103 over Eschenfelder, Baldwin, Ivy, and Oh**

On page 5 of the office action, the examiner rejects claims 26-28 and 33-35 under 35 U.S.C. § 103(a) over Eschenfelder and Baldwin as applied to claims 26-28, and 33 above, and in further view of Ivy (*US 5,720,962*) and Oh (*WO 01/22935*).

Applicants believe that the claim amendments and arguments outlined above, overcome the present rejection. For example, the combination of references also fails to provide any motivation and reasonable expectation of success for arriving at the invention for the reasons provided above. The Ivy and Oh references fail to rectify the deficiencies of the combination of Eschenfelder and Baldwin.

Furthermore, the Oh reference teaches away from the claimed invention of rectal administration, and confirms that there is no motivation to combine the references. Respectfully, the examiner has mischaracterized the Oh reference as teaching “that the administration of common anti-inflammatory compositions to localized regions was known” (p. 10 of the office action). Oh discloses that its composition is “not [applied] to the localized region, but to the palm or other particular parts of the hand” (p. 2 last paragraph to p. 3, line 7 of Oh).

Moreover, the Ivy and Oh references in combination with the Eschenfelder and Baldwin references also fail to provide any predictability regarding rectal administration of a thrombolytic protein to treat hemorrhoid disease, and they fail to compensate for the inoperative teachings of Eschenfelder and Baldwin when the respective additional active compounds are omitted for treatment of hemorrhoid disease.

Applicants respectfully request reconsideration and withdrawal of the rejection.

**Conclusion**

In view of the foregoing amendments and remarks, entry of the amendments and favorable consideration of the claims are respectfully requested. If the examiner has any questions or concerns regarding this amendment, she is invited to contact the undersigned at the telephone number listed below. If any fees are due or any overpayment made in connection with this paper, please charge or credit our Deposit Account No.: 082461.

Respectfully submitted,

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